Cessation of anticoagulation therapy following endovascular thrombus removal and stent placement for acute iliofemoral deep vein thrombosis

Sebastian, Tim ; Engelberger, Rolf P ; Spirk, David ; Hakki, Lawrence O ; Baumann, Frederic A ; Spescha, Rebecca S ; Kucher, Nils

Abstract: Background: The optimal duration of anticoagulation therapy (AT) following catheter-based therapy of acute iliofemoral deep vein thrombosis (IFDVT) with stent placement is unknown. Theoretically, resolving the underlying obstructive iliac vein lesion by a stent may eliminate the main trigger for recurrence, the post-thrombotic syndrome (PTS), and the need for extended-duration AT. Patients and methods: From 113 patients with acute IFDVT who underwent endovascular thrombus removal and stent placement, we compared patency rates and clinical outcomes between 58 patients on limited-duration AT (3–12 month) and 55 patients on extended-duration AT (> 12 months). Results: Mean follow-up duration was 26 ± 18 (range 3–77) months; it was 24 ± 18 (range 3–69) months after cessation of AT in the limited-duration AT group. In comparison to patients with extended-duration AT, patients with limited-duration AT were younger (38 versus 54 years; $p < 0.001$), more often female (74 % versus 49 %; $p = 0.01$), and had less often prior venous thromboembolism (VTE) (9 % versus 35 %; $p = 0.001$). May-Thurner syndrome was more frequent in the limited-duration AT group (66 % versus 38 %; $p = 0.004$). Overall, primary and secondary patency rates at 24 months were 80 % (95 % CI, 70–87 %) and 95 % (95 % CI, 88–98 %), respectively, with no difference between the groups. Overall, 17 (15 %) patients developed recurrent VTE, of which 14 (82 %) events were thrombotic stent occlusions, and 13 (76 %) events occurred during AT. In the limited-duration AT group, 98 % patients were free from the PTS at two years with a VTE recurrence rate of 3.5 per 100 patient years after cessation of AT. Conclusions: In selected patients with acute IFDVT and patent venous stent, particularly in younger and otherwise healthy patients with May-Thurner syndrome, it appears to be safe to discontinue AT 3–12 months after endovascular treatment. Clinical Trial Registration: The study is registered on the National Institutes of Health website (ClinicalTrials.gov; identifier NCT02433054).

DOI: https://doi.org/10.1024/0301-1526/a000774

Cessation of anticoagulation therapy following endovascular thrombus removal and stent placement for acute iliofemoral deep vein thrombosis

Tim Sebastian, MD[*1]; Rolf P. Engelberger, MD[†‡1]; David Spirk, MD[§]; Lawrence O. Hakki, MB[‡]; Frederic A. Baumann, MD[*]; Rebecca S. Spescha, Ph.D.[*]; and Nils Kucher, MD[*]

[*]Clinic for Angiology, University Hospital Zurich, Switzerland
[†]Division of Angiology, Cantonal Hospital Fribourg, Fribourg, Switzerland
[‡]Medical Faculty, University of Bern, Switzerland
[§]Institute of Pharmacology, University of Bern, Switzerland

[1]T.S. and R.P.E. contributed equally to the present work.

Corresponding Author:
Prof. Nils Kucher, M.D.
Director
Clinic of Angiology
University Hospital Zurich
Raemistrasse 100
8091 Zurich, Switzerland
Phone: +41 44 255 33 44
Fax: +41 44 255 43 75
ORCID-ID: 0000-0002-7352-8709
Email: nils.kucher@usz.ch

Abstract

Background:

The optimal duration of anticoagulation therapy (AT) following catheter-based therapy of acute iliofemoral deep vein thrombosis (IFDVT) with stent placement is unknown. Theoretically, resolving the underlying obstructive iliac vein lesion by a stent may eliminate the main trigger for recurrence, the post-thrombotic syndrome (PTS), and the need for extended-duration AT.

Patients and methods:

From 113 patients with acute IFDVT who underwent endovascular thrombus removal and stent placement, we compared patency rates and clinical outcomes between 58 patients on limited-duration AT (3-12 month) and 55 patients on extended-duration AT (>12 months).

Results:

Mean follow-up duration was 26±18 (range 3–77) months; it was 24±18 (range 3–69) months after cessation of AT in the limited-duration AT group. In comparison to patients with extended-duration AT, patients with limited-duration AT were younger (38 versus 54 years; p<0.001), more often female (74% versus 49%; p=0.01), and had less often prior venous thromboembolism (VTE) (9% versus 35%; p=0.001). May-Thurner syndrome (MTS) was more frequent in the limited-duration AT group (66% versus 38%; p=0.004). Overall, primary and secondary patency rates at 24 months were 80% (95%CI, 70-87%) and 95% (95%CI, 88-98%), respectively, with no difference between the groups. Overall, 17 (15%) patients developed recurrent VTE, of which 14 (82%) events were thrombotic stent occlusions, and 13 (76%) events occurred during AT. In the limited-duration AT group, 98% patients were free from the PTS at 2 years with a VTE recurrence rate of 3.5 per 100 patient years after cessation of AT.

Conclusion:

In selected patients with acute IFDVT and patent venous stent, particularly in younger and otherwise healthy patients with MTS, it appears to be safe to discontinue AT 3-12 months after endovascular treatment.

Clinical Trial Registration:

The study is registered on the National Institutes of Health website (ClinicalTrials.gov; identifier NCT02433054).

Keywords

Anticoagulation; catheter-directed thrombolysis; deep vein thrombosis; post-thrombotic syndrome; venous stents

Introduction

Venous thromboembolism (VTE) refers to deep vein thrombosis (DVT) and pulmonary embolism (PE) and is a major cause of morbidity and mortality.(1) Patients with iliofemoral DVT (IFDVT) are at greatest risk of VTE recurrence and the post-thrombotic syndrome (PTS). Compared to patients with DVT located in the popliteal or femoral veins, the rate of recurrent VTE during the initial 3 months of anticoagulation therapy (AT) was twice as high in patients with IFDVT (11.8 versus 5.3%).(2) Furthermore, with conservative therapy up to 30-50% of patients with IFDVT suffer from PTS within 2-8 years after the index event.(3, 4)

Early endovascular thrombus removal therapy, including *catheter-directed thrombolysis* (CDT) and *pharmacomechanical thrombectomy* (PMT), reduces the risk of moderate or severe PTS by removing the occluding thrombus and preventing secondary valve damage.(5-7) Up to 80% of patients with IFDVT have an underlying obstructive iliac vein lesion, which is thought to be the main trigger of thrombosis.(8, 9) The elimination of the obstructing vein lesion by provisional stent placement after early thrombus removal aims at reducing the risk of the PTS and recurrent ipsilateral DVT.(10)

AT is highly effective in preventing thrombus extension and VTE recurrence.(11) According to current consensus statement guidelines, extended duration of AT should be considered in patients with persistent risk factors for recurrence.(12-14) Due to the lack of scientific data, no recommendations regarding post-interventional AT are available in the current guidelines(13-15) and its management is highly inconsistent.(16)

We postulate that in patients with descending IFDVT, early endovascular therapy with subsequent stent placement may reduce the need for extended-duration AT. In the present study, we analyzed patency, VTE recurrence rates, and clinical outcomes of patients with IFDVT following endovascular thrombus removal and stent placement treated with AT for a limited or extended duration.

Methods

Study design

The present analysis was derived from the Swiss Venous Stent registry, an ongoing prospective study consecutively enrolling patients who received venous nitinol stents at the University Clinic of Angiology in Bern since July 2011. From this registry, we included all patients with acute IFDVT who underwent endovascular thrombus removal (CDT and/or PMT) followed by stent placement. Patients <18 years, or with a life expectancy <3 months were excluded. All patients had a minimum follow-up of three months, and at least one duplex ultrasound study. The registry and participant consent form were approved by the Swiss Ethics Committee on research involving humans. The study is registered on the National Institutes of Health website (ClinicalTrials.gov; identifier NCT02433054).

Data and subgroup definitions

For all enrolled patients, baseline demographic information, disease-specific information (thrombosis localization, involved venous segments, symptom onset, recurrence), comorbid conditions, risk factors, and anticoagulation therapy (anticoagulant type, treatment duration, bleeding complications) were recorded using a standardized case report form. Procedural data included type of catheter intervention (CDT/PMT), duration, dose and success of thrombolysis, and type and number of implanted stents.

For the purpose of the present analysis, we predefined two patient subgroups:

1. Limited-duration AT group: Patients with anticoagulation therapy discontinued after 3-12 months of treatment.
2. Extended-duration AT group: Patients with ongoing anticoagulation therapy beyond 12 months.

Diagnosis and initial anticoagulation therapy

IFDVT was objectively confirmed by duplex ultrasound or contrast-enhanced computed tomography. Acute DVT was defined as symptom duration ≤14 days; subacute DVT as symptom duration of 15 to 28 days. On admission, an intravenous bolus of heparin of 80 units per kg body weight was administered. This was omitted, if the patient was already on anticoagulation therapy. Patients with CDT were treated with intravenous heparin administered through the venous access sheath throughout the thrombolysis procedure. Factor Xa levels were monitored frequently to target a factor Xa inhibition activity of 0.3 to 0.7 IU/ml. Within 24 h after full completion of the endovascular therapy, heparin was converted to either VKA (with overlapping LMWH for at least 5 days), rivaroxaban, or to parenteral anticoagulants in patients with active malignancies. The choice of anticoagulation therapy was up to the treating vascular specialist. We did not prescribe antiplatelet therapy after venous stent placement by default, unless otherwise indicated.

Catheter-based therapy

Details on the CDT and PMT procedures have been published previously.(10, 17) Patients with extensive descending IFDVT involving the popliteal veins or the inferior vena cava usually received CDT with a standardized protocol of continuous infusion of 20 mg recombinant tissue plasminogen activator (rt-PA) over 15 hours administered through a conventional lysis catheter (e.g. Craigg-McNamara®, ev3 Endovascular, Plymouth, MN, USA) or the EkoSonic MACH4 Endovascular System (EKOS Corporation, Bothell, Washington). In case of residual thrombi, either prolonged CDT or PMT alone or with high-pressure intraclot injection of 10 mg rt-PA (PowerPulse® technique) using the AngioJet ZelanteDVT® (Boston Scientific, Maple Grove, Minnesota) was performed. Before its market introduction in 2015, AngioJet Solent Omni® (Boston Scientific) was used. In patients with descending IFDVT limited to the

pelvic or proximal femoral veins, single session PMT with an AngioJet® device without prior CDT was an option (17).
After thrombus removal, residual vein lesions were identified by digital subtraction venography (two orthogonal views) or by intravascular ultrasound if venography was equivocal. Significant stenosis was defined by 1) luminal narrowing >50%, 2) absence of antegrade flow, or 3) presence of collateral flow at the site of suspected stenosis. Residual lesions were treated by balloon angioplasty and stent placement. Depending on the affected venous segment and the presence or absence of a compression syndrome, the following stents were used: Sinus-XL® stent for the inferior vena cava, Sinus-Obliquus® May Thurner stent for compressed common iliac veins, Sinus-XL Flex® stent for post-thrombotic iliac or femoral veins (all Optimed, Ettlingen, Germany). Stent diameters were 20–24 mm for the inferior vena cava, 14–16 mm for the iliac veins, 14 mm for the femoral vein.

Clinical follow-up

Clinical follow-up visits were routinely performed at our outpatient clinic by vascular specialists at 3, 6, 12 months, followed by yearly visits. At each visit, symptoms and clinical signs of PTS were recorded using the Villalta score and revised venous clinical severity scores (rVCSS).(18, 19) Current AT and recent VTE complications were assessed. Patients received a standardized duplex sonography examination at each follow-up visit, scanning for thrombotic and post-thrombotic changes of both the treated stent segments and the inflow vessels.

Definition of outcomes

Technical success was defined as antegrade flow and maximal luminal stenosis of ≤30% at termination of the procedure by venography, and evidence of spontaneous flow in the treated vein segment by duplex sonography.(20) *Primary patency rate* was defined as the percentage of patients with primary treatment success and without the occurrence of either thrombosis of the treated segment or re-intervention to maintain patency of the treated segment. *Primary assisted patency includes patients after venous stent placement who developed restenosis, but not occlusive thrombosis, and were successfully retreated. Secondary patency includes also patients after venous stent placement who developed re-occlusion of the stent, and were successfully retreated*.(21)
In order to distinguish between the bleeding complications due to the endovascular intervention and those due to the anticoagulation therapy thereafter, we defined *peri-interventional bleeding complications* as bleeding complications within the first 72 h and *post-interventional bleeding complications* as bleeding complications ≥72 h after the end of the catheter-based treatment. Bleeding complications were classified according to the *International Society on Thrombosis and Haemostasis*, where major bleedings are either 1) fatal bleeding, 2) symptomatic bleeding in a critical area or

organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or 3) bleeding causing a drop in hemoglobin level of 20g/L, or leading to transfusion of ≥2 units of packed red blood cells. Minor bleedings are less severe bleedings not included in the definition of major bleedings.(22)
Presence of PTS was defined as a total Villalta score of ≥5 points, or the presence of a venous ulcer. PTS was classified as mild (Villalta score of 5 to 9 points), moderate (10 to 14 points), or severe (≥15 points, or presence of venous ulcers).

Choice of cessation or continuation of anticoagulation therapy

Cessation of AT was considered if all of the following criteria were fulfilled between 3 and 12 months follow-up: 1) patent venous stents by duplex ultrasound, 2) patent leg inflow veins including the femoral, deep femoral and popliteal veins by duplex ultrasound, and 3) absence of PTS or presence of mild PTS defined as Villalta score < 10 points. The decision on cessation or continuation of AT was revaluated during each office visit and followed, in addition to the above criteria, current consensus guidelines taking into account all of the following criteria: 1) presence of permanent clinical VTE risk factors such as cancer, 2) index event provoked by major surgery or trauma, 3) index event occurred in the presence of May-Thurner syndrome (MTS) or an alternative iliac vein compression syndrome, 4) history of recurrent VTE, particularly if in different locations, 5) known presence of major thrombophilia, i.e. antiphospholipid antibody syndrome or homozygous factor V Leiden mutation, 6) risk of bleeding, 7) patient compliance, and 8) patient preference. For example, AT was usually extended in patients with metastatic cancer or antiphospholipid antibody syndrome or other permanent risk factors, and AT was usually discontinued in younger and otherwise healthy patients, even if no provoking factor except for a MTS was identified.

Statistical analysis
Data are presented as means ± standard deviations or absolute numbers and percentages for continuous and categorical variables, respectively. Categorical outcomes are presented as percentages with 95% confidence intervals (95%CI).
P-values for differences between the groups were calculated from unpaired t-tests or Wilcoxon rank test where appropriate for continuous variables, and chi-square test for categorical variables. The cumulative risks of patency rates were estimated with the Kaplan-Meier method, and compared by use of a univariate Cox-regression analysis. A p-value <0.05 was considered statistically significant. Data were analyzed using STATA 14.1 software (STATACorp LP, College Station, TX, USA).

Results

Baseline characteristics and thrombus extension

A total of 113 patients with a mean age of 45 ± 20 years were included. In comparison to patients with extended-duration AT, patients with limited-duration AT were younger, more frequently of female sex, and less frequently had a personal history of VTE or cardiovascular comorbidities (Table I). All patients had thrombotic occlusion of the common or the external iliac veins, with thrombus extension to the common femoral, deep femoral, femoral, popliteal veins, or the inferior vena cava in 81 (72%), 15 (13%), 55 (49%), 42 (37%), or 23 (20%) patients, respectively, without difference between both study groups.

Procedural data

Primary treatment success was achieved in all patients. Overall, 59 (52%) patients were diagnosed with a May-Thurner syndrome, which was more frequent in the limited duration AT than in the extended-duration AT group [38 (66%) versus 21 (38%); p=0.004). Thrombolysis duration was similar in both groups [17.0 ± 6.1 hours limited-duration AT versus 18.4 ± 8.2 hours extended-duration AT; p=0.31]. Recombinant tissue-type plasminogen activator (rt-PA) doses were significantly lower in patients with limited-duration AT [20.6 ± 6.0 mg versus 23.7 ± 8.9 mg; p<0.04]. Thrombolysis success, mean number of stents [1.7 ± 1.0 stents in the limited-duration AT group versus 1.8 ± 1.3 stents in the extended-duration AT group; p=0.57], and type of postinterventional AT [rivaroxaban: 34 (59%) patients in the limited-duration AT group versus 36 (65%) patients in the extended-duration AT group; VKA: 21 (36%) patients in the limited-duration AT group versus 14 (25%) patients in the extended-duration AT group; others: 3 (5%) patients in the limited-duration AT group versus 5 (9%) patients in the extended-duration AT group; p=0.40] was similar in patients with limited and extended-duration AT. Overall, 22 (19%) of the 113 patients [13 (22%) in the limited-duration AT group versus 9 (16%) in the extended-duration AT group; p=0.66] had a stent extension into the common femoral vein. None of the patients had stent extensions into the deep femoral vein.

Antithrombotic therapy

All patients received anticoagulation therapy for a minimum duration of 3 months. Overall, 70 (62%) patients were treated with rivaroxaban, 35 (31%) with vitamin-K antagonists (VKA), and another 8 (7%) with parenteral anticoagulants including low-molecular-weight heparin, unfractionated heparin, or fondaparinux. All patients with parenteral anticoagulants had active malignancies.

In the limited-duration AT group, AT was terminated at 3, 6, and 12 months in 24 (41%), 19 (31%), and 15 (26%), respectively.

Patency rates

The mean follow-up duration was 26±18 (range 3–77) months, with a longer follow-up duration in the limited-duration AT group (31±17 months) than in the extended-duration AT group (20±18 months; p=0.02). The mean follow-up duration after cessation of AT in the limited-duration AT group was 24±18 (range 3–69). Overall, primary patency rates at 12, 24, and 36 months were 86% (95% CI, 77-91%), 80% (95% CI, 70-87%), and 73% (95% CI, 61-82%), respectively, with no difference between the limited-duration AT group [93% (95%CI, 82-97%), 84% (95%CI, 70-92%), and 77% (95%CI, 60-87%)] and the extended-duration AT group [78% (95%CI, 63-87%), 78% (95%CI, 63-87%), and 71% (95%CI, 51-84%; p=0.16) (Figure 1A).

Overall, primary assisted patency rates at 12, 24, and 36 months were 90% (95%CI, 82-94%), 88% (95%CI, 80-93%), and 84% (95%CI, 73-91%), respectively, with significantly higher patency rates in the limited-duration AT group [97% (95%CI, 87-99%), 94% (95%CI, 84-98%), and 91% (95%CI, 76-97%)] compared to the extended-duration AT group [81% (95%CI, 66-90%), 81% (95%CI, 66-90%), and 74% (95%CI, 54-87%); p=0.04] (Figure 1B).

Overall, secondary patency rates at 12, 24, and 36 months were 96% (95%CI, 90-99%), 95% (95%CI, 88-98%), and 95% (95%CI, 88-98%), respectively, with no significant difference between the limited-duration AT group [100%, 100%, and 100%] and the extended-duration AT group [91% (95%CI, 78-97%), 88% (95%CI, 73-95%), and 88% (95%CI, 73-95%); p=0.82] (Figure 1C).

Outcomes and complications during follow-up

Clinical follow-up data were available in 107 (95%) patients. Overall, 17 (15%) patients developed recurrent VTE during follow-up (equivalent to 7.1 events per 100 patient years), with borderline difference between the limited-duration AT group [5 (9%) patients; 3.3 events per 100 patient years] and the extended-duration AT group [12 (22%) patients; 13.1 events per 100 patient years; p=0.05]. Of these recurrent VTE events, 13 (76%) occurred during AT [1 (2%) in the limited-duration AT group versus 12 (22%) in the extended-duration AT group; p<0.001]; equivalent to 10.2 VTE events per 100 patient years, whereas in the limited-duration AT group 4 (7%) occurred after cessation of AT (equivalent to 3.5 events per 100 patient years). Most of the recurrent VTE events were thrombotic stent occlusions, which occurred in 14 (12%) patients, with no difference between the limited-duration AT group [4 (7%) patients] and the extended-duration AT group [10 (18%) patients; p=0.07]. Patients in the limited-duration AT group had a significant lower risk of developing recurrent VTE [HR 0.27; 95%CI 0.10 - 0.78; p=0.015]. The mean time from intervention to stent thrombosis was 250 ± 268 (range 1 to 890) days. Symptomatic non-fatal PE occurred in 2 (2%) patients, one in each group; and 1 (1%) patient in the extended-duration AT group had a contralateral DVT.

Major non-intracranial bleeding complications occurred in 3 (3%) patients, all in the peri-interventional period, with no difference between the limited-duration AT group [1 (2%) patient] and the extended-duration AT group [2 (4%) patients; p=0.53].
Overall, 92 (86%) patients were free from PTS at latest follow-up, more frequently in the limited-duration AT group [53 (95%) patients] than in the extended duration AT group [39 (76%) patients; p=0.007; Table 3]. At the latest follow-up, mild PTS was present in 14 (13%) patients, with more patients having a mild PTS in the extended-duration AT group than in the limited-duration AT group [11 (22%) patients versus 3 (5%) patients; p=0.02]. None developed a severe PTS or leg ulcers. Overall, the mean Villalta score at the latest follow-up was 1.6±2.1 points, with higher scores in the extended-duration AT group than in the limited-duration AT group (2.3±2.4 points versus 1.0±1.6 points; p=0.001), and the mean rVCSS was 2.4±2.4 points, with higher scores in the extended-duration AT group than in the limited-duration AT group (3.4±2.7 points versus 1.4±1.7 points; p<0.001).

Discussion

In our study, limited-duration AT seems to be a feasible treatment strategy in selected patients with acute IFDVT who underwent early endovascular thrombus removal and treatment of underlying venous obstruction by stent placement, with a low rate of recurrent VTE and PTS after discontinuation of AT.
AT remains the fundament of treatment for all patients with acute proximal DVT, and primarily aims to reduce the risk of thrombus extension, VTE recurrence, and VTE-associated mortality. However, conservative therapy alone with AT and elastic compression stockings is insufficient to prevent the development of a PTS in a high percentage of patients, and patients with acute IFDVT are at greatest risk of recurrent VTE and PTS.(2, 23) Recent randomized-controlled trials – the TORPEDO, CaVenT, and ATTRACT - suggested that endovascular therapy might be more effective in preventing PTS in this population with conflicting results on the rate of VTE recurrence (24-26), but did not provide specific information on the role of AT after endovascular therapy with or without stents. The *2012 Clinical Practice Guidelines of the Society of Vascular Surgery and the American Venous Forum* suggest standard conventional AT after early thrombus removal therapy, but do not provide recommendations for AT after the placement of venous stents(15); the *American Heart Association (AHA)* considers the use of therapeutic anticoagulation with similar dosing, monitoring, and duration as for IFDVT patients without stent as reasonable(27); and the 2012 *American College of Chest Physician (ACCP)* suggests the same intensity and duration of AT as in patients who do not undergo thrombus removal(28), however, AT following endovascular therapy has not been re-addressed in the latest ACCP update in 2016.(14)
It is generally recommended to stop AT after a minimal duration of 3 months in patients with a first-episode proximal DVT related to a major reversible risk factor.(13, 14) Cancer patients and patients with unprovoked DVT or previous VTE should be considered for extended-duration AT (27, 29), since it has been associated with an at

least 80% reduction of recurrence.(30-32) In patients with acute IFDVT, an underlying venous obstruction adds an additional risk factor for recurrent DVT, which is not integrated in the decision-making process by current guidelines.(13, 14, 27, 28) Theoretically, resolving the underlying obstructive vein lesion by a venous stent may eliminate the main trigger for recurrence, the PTS, and the need for extended-duration AT.(10) However, it is unclear whether a venous stent itself presents a further risk factor for re-thrombosis. In our study, 3 of the 58 (5%) patients developed stent thrombosis after cessation of AT, challenging the concept of general stent placement for descending IFDVT. The role of antiplatelet agents for preventing venous stent thrombosis after cessation of AT remains also unclear. Our data show that in selected patients with acute IFDVT treated with endovascular early thrombus removal therapy and venous stent placement, AT can safely be stopped after 3 to 12 months of therapy without an increased VTE rate after stopping. In fact, we report a VTE recurrence rate of 3.5 per 100 patient years after cessation of AT for this subgroup. For comparison, a meta-analysis of 10.050 patients with symptomatic proximal or distal DVT treated with AT only reported a VTE recurrence rate of 7.6 per 100 patient years after cessation of AT, while 3.3% of patients developed recurrent VTE events during active treatment for 6 months.(33) In our study, most thrombotic events occurred during AT, suggesting that stent patency may be influenced by other factors including the status of the femoral inflow veins.

There is currently no consensus on the optimal antithrombotic drug regimen after venous stent placement.(34) A recent study investigated antithrombotic practices after venous stent placement among 106 venous experts in the setting of an acute case of IFDVT due to iliac vein compression: short-duration AT (<3 months), limited-duration AT (3-12 months), and extended-duration AT was reported in 11%, 73%, and 12%, respectively. Four percent of the experts reported antiplatelet therapy only, and 45% reported concomitant use of antiplatelet agents temporarily or life-long after discontinuation of AT.(16) The TORPEDO, CaVenT and ATTRACT trials did not provide specific information on duration of AT in patients who received venous stents.(24-26) In our current practice, antiplatelet therapy is not routinely prescribed after endovascular therapy for acute DVT. The role of antiplatelet drugs during or after stopping AT, or the role of low-dose oral anticoagulants after initial therapeutic dose AT in this particular setting needs to be addressed in future randomized trials.

In our study, most patients remained free from PTS at 2 years in both groups, with a lower rate in the extended-duration AT group than in the limited-duration AT group (72% versus 98%). The difference in baseline VTE risk between the two study groups, such as age and prior VTE (Table I), is the most reasonable explanation for the difference in PTS frequency. Our results are favourable compared to the PTS rates reported in the three aforementioned major randomized controlled trials, ranging between 7% and 43% in the interventional arms.(24-26) A major difference between our study and these trials is certainly the rate of venous stent placement, ranging between 17% and 30% in these trials while in our study cohort all patients were treated with a venous stent. Furthermore, VKAs were the main anticoagulants used in the TORPEDO, CaVenT and ATTRACT trials, whereas rivaroxaban was the most

frequently used anticoagulant in our study. Recent data suggest that the latter may be more effective in preventing the development of PTS.(35, 36)

The strengths of our study encompass the implementation of standard operating procedures for endovascular intervention and the systematic follow-up. To our knowledge, we are the first to provide outcome data for IFDVT patients with stopped AT in the presence of venous stents. However, our study has a number of limitations: First, sample size was moderate. Second, duration of AT was not randomized but determined on an individual basis by treating physicians. Differences in VTE recurrence rates between the groups should be interpreted with caution because patients in the extended-duration AT group more frequently had VTE risk factors as compared to patients with limited-duration AT. Nevertheless, it is important to report clinical outcome data for patients with venous stent implants in the presence and absence of AT. Third, reporting rates of MTS (52%) in our study might be underestimated since diagnosis of iliac vein compression syndromes remain challenging in the presence of acute IFDVT. Fourth, this study was performed in one Swiss tertiary hospital and the results cannot necessarily be extrapolated to other centers or countries. Last, our study is hypothesis generating, and the nature of data does not allow any statement regarding superiority of the various treatments.

In conclusion, in selected patients with acute IFDVT and patent venous stents, particularly in younger and otherwise healthy patients with MTS, it appears to be safe to discontinue AT 3-12 months after endovascular treatment.

Figure 1

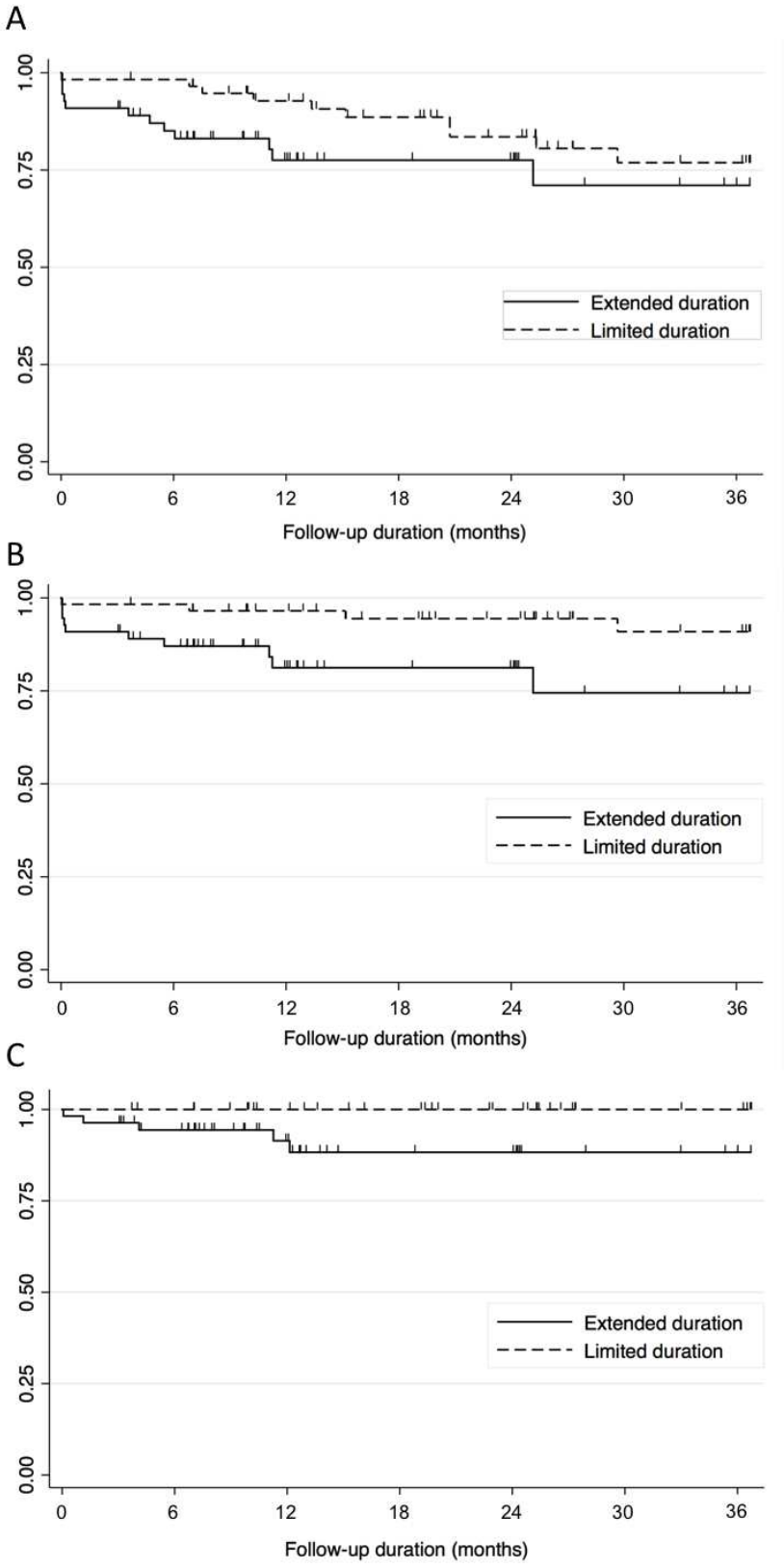
A
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
Follow-up duration (months)
Extended duration
Limited duration
B
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
Follow-up duration (months)
Extended duration
Limited duration
C
1.00
0.75
0.50
0.25
0.00
0
6
12
18
24
30
36
Follow-up duration (months)
Extended duration
Limited duration

Figure 1. Kaplan-Meier curves with primary patency rates (A), assisted primary patency rates (B), and secondary patency rates (C) for the extended-duration AT and limited-duration AT groups. Standard error did not exceed 10%.

Tables

Table I. Baseline characteristics

	Total (n = 113)	Limited-duration AT group (n = 58)	Extended-duration AT group (n = 55)	*P* Value
Demographics				
Age (years)	45.7 ± 20.2	38.1 ± 19.5	53.7 ± 17.8	**<0.0001**
Women	70 (62)	43 (74)	27 (49)	**0.01**
Body mass index (kg/m2)	26.0 ± 5.5	24.9 ± 4.5	27.2 ± 6.1	0.1
Risk factors and comorbidities				
Immobilisation* (< 3 months)	43 (38)	28 (48)	15 (27)	**0.02**
Hormone therapy†	34 (30)	26 (45)	8 (15)	**0.001**
Recent hospitalisation (< 3 months)	26 (23)	18 (31)	8 (15)	**0.04**
Current smoking	25 (22)	15 (26)	10 (18)	0.13
Arterial hypertension	25 (22)	7 (12)	18 (33)	**0.008**
Obesity	24 (21)	8 (14)	16 (29)	0.05
Known previous VTE	24 (21)	5 (9)	19 (35)	**0.001**
Varicose veins / previous surgery for varicose veins	17 (15)	6 (10)	11 (20)	0.15
Known thrombophilia	17 (15)	12 (21)	5 (9)	0.10
Recent surgery (< 4 weeks)	10 (9)	7 (12)	3 (5)	0.23
Dyslipidemia	9 (8)	2 (3)	7 (13)	0.07
Severe infection or sepsis (< 3 months)	9 (8)	6 (10)	3 (5)	0.34
Diabetes	9 (8)	1 (2)	8 (15)	**0.01**
Active cancer or treatment (< 6 months)	8 (7)	2 (3)	6 (11)	0.13
Chronic pulmonary disease	7 (6)	4 (7)	3 (5)	0.75
Recent trauma (< 4 weeks)	7 (6)	6 (10)	1 (2)	0.06
Affected leg				0.07
Left leg DVT	81 (72)	46 (79)	35 (64)	-
Right leg DVT	22 (19)	10 (17)	12 (22)	-
Bilateral DVT	10 (9)	2 (3)	8 (15)	-
Symptoms duration				0.92

Acute (less than 14 days)	99	(88)	51	(88)	48	(87)	-
Subacute (14 to 28 days)	14	(12)	7	(12)	7	(13)	-
Thrombus, involved vein segments							
Inferior vena cava	23	(20)	8	(14)	15	(27)	0.08
Common iliac vein	85	(75)	46	(79)	39	(71)	0.30
External iliac vein	94	(83)	48	(83)	46	(84)	0.90
Common femoral vein	81	(72)	40	(69)	41	(75)	0.51
Femoral vein	55	(49)	26	(45)	29	(53)	0.40
Deep femoral vein	15	(13)	5	(9)	10	(18)	0.13
Popliteal vein	42	(37)	19	(33)	23	(42)	0.32
Lower leg veins	13	(12)	5	(9)	8	(15)	0.32

Note: data presented as mean ± SD or number (%). *defined as bed ridden for > 72h, plaster cast, or long-distance travel of > 6h; †oral contraceptive pill, hormone replacement therapy or Tamoxifen use; AT, anticoagulation therapy; CDT, catheter-directed thrombolysis; DVT, deep vein thrombosis; USAT, ultrasound-assisted catheter-directed thrombolysis; VTE, venous thromboembolism

Table II. Clinical outcomes

	Total (n = 113)	Limited-duration AT group (n = 58)	Extended-duration AT group (n = 55)	*P* Value
At 6-month follow-up	**n=93**	**n=49**	**n=44**	
Mean Villalta score	1.6 ± 2.0	1.0 ± 1.2	2.2 ± 2.4	**0.003**
No PTS	84 (90)	49 (100)	35 (80)	**0.02**
Mild PTS	8 (9)	0 (0)	8 (18)	**0.002**
Moderate PTS	1 (1)	0 (0)	1 (2)	0.49
Severe PTS	0 (0)	0 (0)	0 (0)	-
Mean rVCSS	2.5 ± 2.2	1.9 ± 1.8	3.2 ± 2.4	**0.005**
At 12-month follow-up	**n=86**	**n=50**	**n=36**	
Mean Villalta score	1.5 ± 1.7	1.1 ± 1.3	2.0 ± 1.9	**0.01**
No PTS	81 (94)	50 (100)	31 (86)	**0.01**
Mild PTS	5 (6)	0 (0)	5 (14)	**0.01**
Moderate PTS	0 (0)	0 (0)	0 (0)	-
Severe PTS	0 (0)	0 (0)	0 (0)	-
Mean rVCSS	2.1 ± 2.1	1.2 ± 1.3	3.3 ± 2.5	**<0.0001**
At 24-month follow-up	**n=58**	**n=40**	**n=18**	
Mean Villalta score	1.6 ± 2.2	1.1 ± 1.5	2.9 ± 3.0	**0.003**
No PTS	52 (90)	39 (98)	13 (72)	**0.009**
Mild PTS	5 (9)	1 (2)	4 (22)	**0.03**
Moderate PTS	1 (1)	0 (0)	1 (6)	0.31
Severe PTS	0 (0)	0 (0)	0 (0)	-
Mean rVCSS	2.2 ± 2.7	1.4 ± 1.9	4.3 ± 3.3	**0.0001**

Note: data presented as mean ± SD or number (%). AT, anticoagulation therapy; PTS, post-thrombotic syndrome; rVCSS, revised venous clinical severity score